TITLE: Prospective study in 355 patients with suspected COVID-19 infection. Value of cough, subjective hyposmia, and hypogeusia

RUNNING TITLE: Cough, subjective hyposmia, hypogeusia and COVID-19.

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ABSTRACT

OBJECTIVE. To evaluate the incidence of certain symptoms in a population of health workers exposed to COVID-19 patients.

METHODS: A case-control study was conducted at a tertiary care hospital from March 1 to April 7, 2020. Health workers with suspected COVID-19 infection were included. The presence of COVID-19 was detected by using real-time-PCR methods. Positive and negative RT-PCR patients were used as case and control groups, respectively.
This study analyzed the incidence of COVID-19 symptoms in both patient groups. Visual analog scales were used for self-assessment of smell and taste disorders, ranging from 0 (no perception) to 10 (excellent perception).

RESULTS. There were 215 (60.6%) patients with positive RT-PCR and 140 (39.4%) patients with negative RT-PCR. The presence of symptoms such as hyposmia hypogeusia, dysthermia and cough were strongly associated with a positive RT-PCR. The association of cough and subjective hyposmia had 5.46 times higher odds of having a positive test. The ROC analysis showed that a fever higher than 37.45 ºC, resulted in sensitivity and specificity of 0.65 and 0.61, respectively. A total of 138 cases (64.1%) and 114 cases (53%) had subjective hyposmia and hypogeusia respectively. The 85.4% of these patients recovered olfactory function within the first 14 days of the onset of the symptoms.

CONCLUSIONS: There is a significant association between positive PCR and subjective hyposmia. The association of subjective hyposmia and cough, increase significantly the odds of having a positive RT-PCR. The measurement of fever as the only method for screening of COVID-19 infection resulted in a poor association.

KEYWORDS: Hyposmia, hypogeusia, COVID-19, Odds ratio, incidence, ROC.

Level of evidence: 3

INTRODUCTION

Since the first group of cases of coronavirus disease infection (COVID-19) was reported in Wuhan, China, in late December 2019, the disease has spread widely in the past 4 months, resulting in a global pandemic with an increasing number of deaths, affecting practically every country in the world[1].

The spread from China was initially to other Asian countries, primarily to the Republic of Korea, then to the Middle East, most notably to Iran, then to southern Europe, especially Italy and Spain[2] and then to the most recent epicenter, the US.

Currently, there are fewer cases reported in low- and middle-income countries, but these are likely to increase dramatically in these countries, especially where medical care is limited, and fewer diagnostic tests are performed.

While there has been regular monitoring and reporting of total cases and deaths worldwide, numbers of different types of workers exposed in the workplace are less known. Workers involved in health care are at the forefront for risk of infection and death, as has been the case during many previous infectious disease epidemics, such as severe acute respiratory syndrome (SARS) and Ebola[3].

In the management of the health crisis, the identification of paucisymptomatic patients is emerging as a crucial factor to interrupt the virus 'chain of transmission, since this symptomatology may represent the only manifestation of the disease.

In health centers dealing with this emergency, a significant number of patients presenting hyposmia, hypogeusia[4], mild headache, diarrhea, or odynophagia[5] associated with fever (> 37.5 ° C) are not correctly identified as potentially infected with COVID-19.

The actual incidence of these symptoms is not adequately described in the reviews that have been carried out, with very wide ranges according to the different authors. Odynophagia, for example, is present in 5% to 17.4% of patients with COVID-19[6,7]. Hyposmia has been reported in 5.1% to 19.4% of cases[4].

This large variation maybe because most of the patients included in these reviews[8] were drawn from studies that did not accurately describe the clinical presentation [9,6]. The largest report on 44672 confirmed patients with COVID-19 focused on critical cases and case fatality rate, without a detailed presentation of symptoms. In contrast, other studies that described the full spectrum of symptoms of COVID-19 found that sore throat or hyposmia was not uncommon[4,5].

Early reports have suggested that acute smell loss may be an early symptom associated with the worldwide pandemic known as COVID-19[10]. Also, smell, and/or taste loss has been noted in the absence of other known symptoms of the disease, but they have yet to be verified with hard data, including testing of both smell function and/or COVID-19[11]. Currently, polymerase chain reaction (PCR) is the standard for the detection of SARS-CoV-2 from nasal and oropharyngeal exudate [12]. The results of these tests could be affected by the variation of the viral RNA sequences or by the viral load in different anatomical sites during the evolution of the disease [12].

A recent study of 1014 cases of COVID-19 found that only 59% of patients had positive PCR in cases of SARS-CoV-2 at the onset of symptoms, while chest CT had a higher sensitivity for the diagnosis of COVID-19[13].

Consequently, the clinical presentation could be useful in identifying suspected cases of COVID-19, and we believe that mild symptoms such as sore throat, hyposmia, or hypogeusia should not be considered a rare symptom.

Methods

We performed a case-control study from March 15 to April 7, 2020. Inclusion criteria were health workers of the University Hospital of Getafe with suspicion of COVID-19 infection. Exclusion criteria were inconclusive PCR results.

The suspicion of COVID-19 was determined by the presence of either cough, fever (>37.5ºC), headache, or breathlessness of any health worker regardless of contact with a COVID-19 patient.

This project was approved by the institutional review board (CV20/24). Patient informed consent was obtained in every patient.

We collected clinical data from the anamnesis, especially focused on every symptom associated with COVID-19 infection (Figure 1). Visual analog scales were used for self-assessment of smell and taste, ranging from 0 (no perception) to 10 (excellent perception). Demographic data such as age and sex were reviewed. We reviewed the medical records of these patients to evaluate the incidence of other cranial neuropathies and possible predisposing factors of cranial nerve susceptibility, such as smoking, diabetes mellitus (DM), hypertension, or dyslipidemia.

Fever was defined as a body temperature above 37.5 degrees Centigrade, measured by an axillary digital thermometer.

The presence of COVID-19 in respiratory specimens, from nasal and pharyngeal swabs, was detected by next-generation sequencing or real-time RT-PCR methods. Allplex™ 2019 -

nCoV Assay (Seegene) is a multiplex real-time PCR assay for simultaneous detection of 3 target genes of SARS-CoV-2 in a single tube. The assay is designed to detect RdRP, N genes specific for SARS-CoV-2, and E gene for all Sarbecovirus including SARS-CoV-2.

Cases were defined as those patients with a positive RT-PCD while patients with a negative test, were the controls.

Every case was subsequently evaluated at the two weeks follow up, with a new anamnesis and RT-PCR.

Statistical Analysis Statistical Package for the Social Sciences for Windows (SPSS version 25.0; IBM Corp, Armonk, NY, USA) was used to perform the statistical analyses. The potential associations between epidemiological, clinical, and olfactory and gustatory outcomes have been assessed through cross-tab generation between two variables (binary or categorical variables) and Chi-square test. Categorical variables between both age and sex-matched groups were summarized by counts and frequencies and compared using odds ratio (OR) with 95% CIs. The relationship between VAS variables was investigated using Spearman's correlation coefficient.

A receiver operating characteristic (ROC) curve was used to determine the cutoff values of the degrees Centigrade and positive RT-PCR patients. The area under the ROC curve (AUC) varies from 0.5 for random performance to 1.0 for perfect performance.

The normally distributed variables were presented with means and SDs.

Results

Demographic data

A total of 355 patients participated in this study. The mean age of patients was 42.9 ± 0.67 years (range 18–65). There were 287(80.8%) females and 154(19.2%) males.

There were 215 (60.6%) patients with positive RT-PCR and 140 (39.4%) patients with a negative RT-PCR, as part of the control group.

The most prevalent comorbidities of patients were hypertension, dyslipidemia, asthma, and hypothyroidism. There were no significant differences in baseline demographic characteristics, including age, sex or comorbidities, between both cases and controls groups

The mean time between the onset of the symptoms and the evaluation was 7.8 ± 0.51 days and 7.27 ± 0.60 days, in cases and controls, respectively, with no statistically significant differences.

Association between general symptoms and COVID-19 infection

The general symptoms of patients are described in Figure 1. Asthenia, cough, myalgia, headache, subjective hyposmia, hypogeusia, back pain and dysthermia were the most prevalent symptoms, accounting for more than 50% of patients.

The presence of certain symptoms such as subjective hyposmia (OR 4.88), hypogeusia (OR 3.51), dysthermia (OR 2.38), and cough (OR 1.83) was strongly associated with a positive RT-PCR. The association of cough and subjective hyposmia had 5.46 times higher odds of having a positive test. In the same way, patients with both dysthermia and subjective hyposmia had 3.91 times higher odds of having an RT-PCR (Table 1).

Other symptoms such as myalgia, asthenia, rhinorrhea, back and chest pain, dyspnea, diarrhea, headache, and sore throat were not associated with increased odds of being infected with COVID-19.

Finally, the presence of fever (measured temperature greater than 37.5° C) had 3.13 times higher odds of having a positive RT-PCR than afebrile patients.

To assess the optimal cutoff point between the degrees centigrade and a positive RT-PCR we performed a ROC analysis with an area under the curve of 0.671 (p=0.001). The ROC analysis showed that a fever higher than 37.45 °C, results in sensitivity and specificity of 0.65 and 0.61, respectively (Fig.2).

Subjective hyposmia and hypogeusia

Regarding olfactory and taste function, a total of 138 cases (64.1%) and 114 cases (53%) had subjective hyposmia and hypogeusia respectively. The cases presented significantly lower olfactory and taste VAS scores compared to controls (p<0.001), as observed in Table 2. There was a significant positive association between both symptoms ($p < 0.001$), and their VAS were highly correlated (r2=0.714).

Regarding the association of any other symptom to the subjective hyposmia or hypogeusia, 159 (70.9%) patients associated more than two symptoms, 50 (22.3%) patients had at least two symptoms, 12 (5.3%) patients associated 1 and 3 patients (1.3%) didn't associate any symptom.

There was no significant association between comorbidities and the development of subjective hyposmia or hypogeusia. Olfactory dysfunction was not significantly associated with rhinorrhea or nasal obstruction.

Residual symptoms

Fourteen patients (3.94%) developed pneumonia or severe symptoms which required hospitalization. One hundred and sixty-four patients (76.3%) totally recovered from their symptoms at the two weeks follow up. The mean time of recovery was 10.66±0.44 days.

We did not observe any significant association between comorbidities or any symptom with the time to recover.

Considering the patients with a clinically resolved infection at the two weeks follow-up, 51 patients (23.8%) still had residual symptoms. The most frequently reported residual symptom was cough (11.2%) followed by subjective hyposmia (10.7%), and headache (1.9%).

The short-term olfaction recovery rate was assessed in 123 clinically cured patients. 85.4% of these patients recovered olfactory function within the first 14 days of the onset of the symptoms.

Discussion

This is the first case-control study that analyzes the odds of patients having a positive RT-PCR.

Our health care personnel are essential workers defined as paid persons serving in our health care settings who have the potential for direct or indirect exposure to patients or infectious materials.

Worldwide, as millions of people stay at home to minimize the transmission of severe acute respiratory syndrome coronavirus, health-care workers prepare to do the exact opposite. They go to clinics and hospitals, putting themselves at high risk for COVID-2019[2].

In addition to healthcare workers, there are many other types of workers who are at increased risk of infection, generally because they are close to being infected. These include emergency services personnel, workers employed in nursing homes, daycare or education workers, cleaners, the hotel industry, public transportation, and drivers, to name a few. The importance of our results lies in the fact that they can be extrapolated to those other types of workers. The safety of that personnel is essential, to provide the best possible services for infected persons. It is, therefore, crucial to identify those positive health workers, to isolate them in their homes.

It is widely recognized that screening is an imperfect barrier to spread [14] usually due to the lack of detectable symptoms during the incubation period, variation in the detectability of symptoms, and imperfect performance of screening equipment or personnel [15].

Concerning the prevalence of general symptoms, our results are similar to other recent studies [7, 10]. Nevertheless, those studies do not predict or estimate the possibility of having a COVID-19 infection. For example, symptoms, such as myalgia, asthenia, back and chest pain, diarrhea, or headache, which were present in a large percentage of our cases, did not have a

significant result in predicting a COVID-19 infection, because they were also highly present in our control group.

In the same way, the detection of measured fever, usually employed as a screening method, had an AUC of 0.671 and a sensitivity and specificity of 0.65 and 0.61, respectively, which are far from being optimal. In our opinion, this should be considered when creating screening plans, or in case that diagnostic tests are not completely available for the general population. Coronavirus has already been identified as a family of viruses that may be associated with anosmia [16], and it has been demonstrated on transgenic mice that SARS-CoV may enter the brain through the olfactory bulb, leading to rapid transneuronal spread [17]

International reports are accumulating from otolaryngologists and other health-care workers on the front lines that anosmia, with or without dysgeusia, are symptoms frequently associated with COVID-19 infection [18]. The American Academy of Otolaryngology-Head and Neck Surgery and the British Association of Otorhinolaryngology is now recommending these symptoms be added to the list of primary screening symptoms for COVID-19. Although the onset of the viral associated olfactory loss is sudden, patients rarely pay attention to this symptom, given the common co-occurrence of other associated symptoms [19]. Therefore, is often a delay between the onset of the olfactory loss and the patient's perception [20].

Recent retrospective studies [10, 21] reported more than 80% of patients having olfactory dysfunction, supporting the role of otolaryngologists as the first-line physicians for some COVID-19 patients. In our population, 64.1% and 53% of our cases, had subjective hyposmia and hypogeusia respectively, which is a significantly lower percentage, probably due to the retrospective design of their study.

In our prospective study, there was a significant association between the positive PCR and subjective hyposmia. This seems to represent the fact that, based on the odds ratio, the odds of patients having a positive RT-PCR, were 4.88 times higher if they had subjective hyposmia. Interestingly, if we consider the association of subjective hyposmia and cough, the odds increase significantly to 5.46, which may be of interest when designing clinical tools to identify COVID-19 patients. The novelty of this finding is now diminished, in that the WHO has already adopted this finding. However, these data do provide another analysis in a specific population of at-risk subjects.

Regarding the association with other symptoms, the incidence of isolated subjective hyposmia or hypogeusia was present in just 1.3% of our population. Therefore, we consider

that clinical scenario as marginal. The differences with other reports are probably related to a lack of awareness of those mild symptoms among both patients and clinicians [20, 11].

In most cases, these episodes of smell loss are self-limiting. In our population, 85.4% of these patients recovered olfactory function within the first 14 days of the onset of the symptoms. The fact of persistent subjective hyposmia is presumed to occur through a more direct olfactory insult by the virus [11].

However, given the scale of this pandemic, if COVID-19 does cause a chronic olfactory loss in even a small portion of those infected, then the overall population prevalence could be quite large. It is important to highlight that results from olfactory testing of subjects may impact these conclusions, since there is known to be a poor correlation between subjective reporting and objective chemosensory testing[22].

Our population of cases should be considered paucisymptomatic patients, because of the benign evolution of the disease. 76.3% of our cases had total recovery of their symptoms at the two weeks follow up, which represents the majority of our cases. Less than 4% of our patients developed pneumonia, and just 23.8% of our cases, still had minor residual symptoms, such as cough, subjective hyposmia or headache. It is precisely those paucisymptomatic and asymptomatic patients, who represent the major challenge to the medical system, to identify them and avoid further spread of the pandemic.

The main limitation of our study results from our health workers' population. Since they were attended in case of suspicion of a COVID-19 infection, our percentage of totally asymptomatic subjects is probably abnormally low. In the same way, we should emphasize that our high percentage of the female population (81%) should prevent generalizing our results to other male populations.

Case-control studies are limited usually by issues with the identification of controls and the possible biases this may introduce, as well as reporting bias. In a prospective case-control study, this bias is usually limited and is unlikely to have affected our results.

Despite the limitations, the data presented here may constitute a valuable help for future prospective studies with longer follow up periods investigating these associations. In the same way, performing objective smell testing on these patients may give us new information and conclusions that would add value to the scientific literature.

Conclusions

There is a significant association between positive PCR and subjective hyposmia.

If we consider the association of subjective hyposmia and cough, the odds of having a positive RT-PCR increase significantly.

The measurement of fever as the only method for screening of COVID-19 infection results in a poor association.

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Figure legends and tables

Figure 1. Symptoms associated with COVID-19 infection. The ordinate axis consists of

percentages of patients

Figure 2. Receiver operating characteristic (ROC) curve showing the capacity of degrees
centigrade increase in predicting a positive PCR for COVID-19. The area under the curve
was 0.671. The analysis showed that a fever higher than 37.45 ºC, results in sensitivity and
specificity of 0.65 and 0.61, respectively.

Table 1. Description of case and control groups

Table 2. Symptoms of Cases and Controls

Symptoms	Odds Ratio (95% CI)	Significance (p)
Cough+Hyposmia	**5.46(3.02-9.88)**	**0.000**
Hyposmia	**4.88(2.89-8.24)**	**0.000**
Dysthermia+Hyposmia	**3.91(2.08-7.30)**	**0.000**
Hypogeusia	**3.51(2.09-5.89)**	**0.000**
Dysthermia	**2.38(1.49-3.79)**	**0.000**
Cough	**1.83(1.08-3.11)**	**0.029**
Myalgia	1.53(0.91-2.58)	0.10
Asthenia	1.19(0.64-2.14)	0.56
Rhinorrhea	1.04(0.64-1.70)	0.85
Back pain	0.92(0.56-1.5)	0.74
Chest pain	0.88(0.54-1.44)	0.62
Dyspnea	0.86(0.53-1.39)	0.54
Diarrhea	0.77(0.49-1.21)	0.26
Headache	0.74(0.42-1.29)	0.29
Sore throat	**0.59(0.36-0.95)**	**0.03**

Variable	Positive RT-PCR No.(%)	Negative RT-PCR No.(%)	Significance (p)
Sex			0,43
Male	44 (20,5%)	24 (17,1%)	
Female	171 (79,5%)	116 (82,9%)	
Hyposmia	138 (64.1%)	30 (24,8%)	**<0.001**
VAS 0-2	78 (56.5%)	12(40%)	**<0.001**
VAS 3-5	33 (23.9%)	11 (36,7%)	**<0.001**
VAS 6-8	20 (14.4 %)	2 (6,7%)	**<0.001**
VAS 9-10	7 (5.1%)	5 (16,6%)	**<0.001**
Rinorrhea	61(51,3%)	14 (53,8%)	0,811
Hypogeusia	114 (53%)	25 (17,9%)	**<0.001**
VAS 0-2	65(57%)	9(36%)	**<0,001**
VAS 3-5	31 (27,2%)	5(20%)	**0,003**
VAS 6-8	15 (13,1%)	7(28%)	**<0,001**
VAS 9-10	3 (2,6%)	4 (16%)	**<0,001**
Rinorrhea	54(51,4%)	14(28,3%)	0.541

ROC Curve